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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/716,174	11/17/2003	Quan Nguyen	70-000150US	3901
22798 7590 06/14/2007 QUINE INTELLECTUAL PROPERTY LAW GROUP, P.C. P O BOX 458 ALAMEDA, CA 94501			EXAMINER YU, MELANIE J	
			ART UNIT 1641	PAPER NUMBER
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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

**Office Action Summary**

Application No.

10/716,174

Applicant(s)

NGUYEN ET AL.

Examiner

Melanie Yu

Art Unit

1641

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --  
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) ☒ Responsive to communication(s) filed on 07 May 2007.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) ☒ Claim(s) 1,3-10,13-19,21-56,61,201-221 and 304-307 is/are pending in the application.
- 4a) Of the above claim(s) 14-17,201-221 and 304-307 is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1,3-10,13,18,19,21-25,29-32,47-56,61 and 308 is/are rejected.
- 7) ☒ Claim(s) 26-28 and 33-46 is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

**Application Papers**

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 17 November 2003 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- \* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

- |  |   |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892)                                | 4) <input type="checkbox"/> Interview Summary (PTO-413)<br>Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)                       | 5) <input type="checkbox"/> Notice of Informal Patent Application                       |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)<br>Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____  |

Art Unit: 1641

### **DETAILED ACTION**

1. Applicant's after final amendment and arguments filed 7 May 2007 have been entered.

#### ***Election/Restrictions***

1. Newly submitted claims 304-307 are directed to an invention that is independent or distinct from the invention originally claimed for the following reasons: the new claims require the substrate not converted to the second state by cleavage by the enzyme, which is not required of the rejected claims and the rejected claims require the sensor and enzyme to be comprised by a cell, which is not required of new claims 304-307.

Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claims 304-307 are withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

#### ***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

Determining the scope and contents of the prior art.  
Ascertaining the differences between the prior art and the claims at issue.  
Resolving the level of ordinary skill in the pertinent art.  
Considering objective evidence present in the application indicating obviousness or nonobviousness.

Art Unit: 1641

2. Claims 1, 3-5, 7-8 and 308 are rejected under 35 U.S.C. 103(a) as being unpatentable over Burbaum et al. (US 5,981,207) in view of Walker et al. (Signaling pathways underlying eosinophil cell motility revealed by using caged peptides, 1998, PNAS, pg 1568-1573) further in view of Ting et al. (Genetically encoded fluorescent reporters of protein tyrosine kinase activities in living cells, 2001, PNAS, Vol. 98, no. 26, pages 15003-15008).

Burbaum et al. teach an enzyme (col. 7, lines 44-48; kinase, col. 21, lines 50-57) and a substrate for the enzyme (col. 7, lines 39-43), wherein the substrate is in a first state on which the enzyme can act (col. 7, lines 45-47), thereby converting the substrate to the second state (col. 7, lines 43-47), and a first label, wherein a first signal is exhibited by the first label when the substrate is in the first state and is distinguishable from a second signal exhibited by the first label when the substrate is in its second state (col. 11, lines 38-41); and one or more first caging groups associated with the one or more molecules, the first caging groups inhibiting the enzyme from acting upon the substrate and wherein an induced conformational change (release) in the first caging groups permits the enzyme to act upon the substrate (col. 7, lines 39-47). Burbaum et al. fail to teach the enzyme and sensor being in a cell.

Walker et al. teach a caged peptide synthesized outside of a cell and subsequently injected in a cell, in order to provide rapid detection results with good spatial resolution (pg. 1568, right column-left column, first paragraph).

Ting et al. teach a composition comprising: a cell (characterization in mammalian cells, pg. 15003, right column, second paragraph): an enzyme (kinase activity is detected in the cell, therefore the enzyme is in the cell, pg. 15005, right column, cellular response of the Src Reporter) and a sensor, wherein the sensor comprises: a substrate for the enzyme wherein the substrate is in a first state on which the enzyme can act, thereby converting the

Art Unit: 1641

substrate to a second state (substrate undergoes significant conformational change, pg. 15003, left column, first paragraph), and a first label, wherein a first signal is exhibited by the first label when the substrate is in its first state and is distinguishable from a second signal exhibited by the first label when the substrate is in its second state (pg. 15003, left column, last paragraph-right column, first paragraph), in order to study kinase and phosphatase functions, localization and activities inside living cells.

Therefore it would have been obvious to one having ordinary skill in the art at the time the invention was made to include the sensor of an enzyme of Burbaum et al., in a cell as taught by Walker et al., in order to provide injection into a cell and give time to allow the substrate to distribute evenly so normal cell activity can be detected as taught by Walker et al. and to image localization and activities inside living cells as taught by Ting et al.

Regarding claims 3-5, the claims are drawn to intended use of a composition and do not appear to require any further physical limitations. Therefore, since all physical limitations required for the composition as recited in claim 1 are taught by Burbaum et al. in view of Walker et al. further in view of Ting et al., as described above, the composition of Burbaum et al. in view of Walker et al. further in view of Ting et al. is capable of providing the uses recited in claims 3-5.

With respect to claims 7-8, Burbaum et al. teach the caging groups being covalently attached to the enzyme substrate, wherein the caging groups are photolabile and are removed by exposure to light of 366 nm (col. 22, lines 40-55), which is encompassed by the range of between about 60 nm and about 400 nm.

3. Claims 1, 3-6, 9, 10, 18, 21, 23-25, 29-32 and 308 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ting et al. (Genetically encoded fluorescent reporters of protein tyrosine kinase activities in living cells, 2001, PNAS, Vol. 98, no. 26, pages 15003-

Art Unit: 1641

15008) in view of Burbaum et al. (US 5,981,207) further in view of Walker et al. (Signaling pathways underlying eosinophil cell motility revealed by using caged peptides, 1998, PNAS, pg 1568-1573) and Ladner et al. (US 2003/0219722).

Ting et al. teach a composition comprising: a cell (characterization in mammalian cells, pg. 15003, right column, second paragraph): an enzyme (kinase activity is detected in the cell, therefore the enzyme is in the cell, pg. 15005, right column, cellular response of the Src Reporter) and a sensor, wherein the sensor comprises: a substrate for the enzyme wherein the substrate is in a first state on which the enzyme can act, thereby converting the substrate to a second state (substrate undergoes significant conformational change, pg. 15003, left column, first paragraph), and a first label, wherein a first signal is exhibited by the first label when the substrate is in its first state and is distinguishable from a second signal exhibited by the first label when the substrate is in its second state (pg. 15003, left column, last paragraph-right column, first paragraph). Ting et al. fail to teach one or more first caging groups associated with the one or more molecules.

Burbaum et al. teach a caged enzyme substrate, wherein the first caging group prevents the enzyme from acting on the substrate and release of the first caging group permits the enzyme from acting on the substrate (col. 7, lines 36-47), in order to release the substrate into an activated for at an appropriate time.

Walker et al. teach a caged peptide in a cell, in order to provide rapid detection results with good spatial resolution (pg. 1568, right column-left column, first paragraph).

Ladner et al. teach producing a protein *in vivo* or synthetically, *in vitro* (par. 811), in order to compare the signal sequence of two different proteins.

Therefore it would have been obvious to one having ordinary skill in the art at the time the invention was made to include in the composition of Ting et al., the substrate being caged as taught by Burbaum et al., in order to provide injection into a cell and give time to

Art Unit: 1641

allow the substrate to distribute evenly so normal cell activity can be detected as taught by Walker et al. It would have been obvious to apply the teachings of caging chemically synthesized peptides as taught by Burbaum et al. and Walker et al. with the teaching of a peptide produced in vivo as taught by Ting et al. because Ladner et al. teach that a protein may be produced either in vivo or in vitro. Therefore the protein of Ting et al. may be made in vitro as taught by Ladner et al. and injected into a cell as taught by Walker et al. instead of being produced in vivo.

With respect to claim 6, Ting et al. also teach the label being an optically detectable label and the second signal being a fluorescent signal that has a greater intensity than the first signal (FRET change creates fluorescent signal after conformational change and reverses the FRET change prior to conformational change (pg. 15003, left column, last paragraph-right column, first paragraph).

Regarding claims 3-5, the claims are drawn to intended use of a composition and do not appear to require any further physical limitations. Therefore, since all physical limitations required for the composition as recited in claim 1 are taught by Ting et al. in view of Burbaum et al. further in view of Walker et al., as described above, the composition of Ting et al. in view of Burbaum et al. further in view of Walker is capable of providing the uses recited in claims 3-5.

With respect to claims 7-8, Burbaum et al. teach the caging groups being covalently attached to the enzyme substrate, wherein the caging groups are photolabile and are removed by exposure to light of 366 nm (col. 22, lines 40-55), which is encompassed by the range of between about 60 nm and about 400 nm.

Regarding claims 9, 10 and 18, Ting et al. teach the first label and the substrate being physically connected (YFP and CFP are attached to the substrate peptide, pg. 15004, Figure 1a), the substrate being a polypeptide (substrate is shown as a peptide, pg. 15004,

Art Unit: 1641

Fig. 1a) and the enzyme being a protein kinase that phosphorylates serine/threonine and tyrosine (design works for serine/threonine and tyrosine kinases, pg. 15008, left column, second paragraph).

With respect to claims 21 and 29, Ting et al. in view of Burbaum et al. further in view of Walker et al. as applied to claims 1 and 18, teach the limitations of the claim. Ting et al. further teach the polypeptide comprising a second label wherein the first and second labels interact to produce the first signal when the substrate is not phosphorylated and a second signal when the substrate is phosphorylated (pg. 15004, Fig. 1a; pg. 15003, left column, last paragraph-right column, first paragraph).

Regarding claims 23 and 31, Ting et al. teach the first label located at the N-terminus of the polypeptide and the second label located at the C-terminus end of the polypeptide (pg. 15004, Fig. 1a).

With respect to claims 24 and 32, Ting et al. teach the first and second labels being fluorophores capable of exhibiting FRET (pg. 15003, left column, last paragraph-right column, first paragraph).

Regarding claim 25, Ting et al. teach the phosphorylation of the substrate triggers a conformational change in the polypeptide causing a FRET change between the first label and the second label (pg. 15003, left column).

4. Claims 13, 19, 22, 30 and 61 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ting et al. (Genetically encoded fluorescent reporters of protein tyrosine kinase activities in living cells, 2001, PNAS, Vol. 98, no. 26, pages 15003-15008) in view of Burbaum et al. (US 5,981,207) further in view of Walker et al. (Signaling pathways underlying eosinophil cell motility revealed by using caged peptides, 1998, PNAS, pg 1568-1573) and Ladner et al. (US 2003/0219722), as applied to claims 1, 21 and 29, and Kris et al. (US 2003/0096232).



Art Unit: 1641

Ting et al. in view of Burbaum et al. further in view of Walker et al. and Ladner et al., teach a composition comprising an enzyme substrate, a first label and a first caging group, but fail to teach the substrate being specific for a protease and the location of the first label on the polypeptide.

Kris et al. teach detection of enzyme activity wherein a substrate is specific for a kinase or a protease (par. 18 and 78), in order to provide a surface that can detect the activity of a plurality of enzymes.

Therefore it would have been obvious to one having ordinary skill in the art at the time the invention was made to include in the composition of Ting et al. in view of Burbaum et al. further in view of Walker et al., a protease as the enzyme as taught by Kris et al., in order to identify potential blood thinners or agents which cause blood clots.

Regarding claim 19 and 22, Kris et al. also teach a polypeptide substrate (par. 18-19), wherein the one polypeptide comprises a first label and substrate for kinase (labeled antibodies bind to substrate, and therefore a single polypeptide comprises the substrate and first label, par. 256-258), the substrate comprising a tyrosine residue capable of being phosphorylated by the kinase (par. 256), wherein the first label is located at the tyrosine residue and exhibits a first signal when the residue is not phosphorylated and the second signal when the signal is phosphorylated (labels bind to phosphorylated substrates, and therefore bind to the phosphorylated residues, par. 258).

With respect to claim 61, Ting et al. teach a kit comprising a substrate and a first label (col. 3, lines 16-23). Burbaum et al., as described above, teach a caging group, and Kris et al. teach including instructions for use in a kit (par. 84-87).

5. Claims 47-56 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ting et al. in view of Burbaum et al. further in view of Walker et al. and Ladner et al., as applied to claim 1, and Fischer et al. (Cellular Delivery of Impermeable Effector Molecules in the

Art Unit: 1641

Form of conjugates with Peptides capable of mediating membrane translocation, 2001, Bioconjugate Chemistry, Vol. 12, No. 6, pages 825-841).

Ting et al. in view of Burbaum et al. further in view of Walker et al. and Ladner et al., teach a sensor comprising one or more molecules, but fail to teach the one or more molecules associated with a cellular delivery module.

Fischer et al. teach delivery polypeptide vectors are used to transport entire proteins into a cell (pg. 827, right column, second paragraph), in order to provide delivery of proteins that are longer than a few peptides into a cell.

Therefore it would have been obvious to one having ordinary skill in the art at the time the invention was made to include in the substrate of the composition of Ting et al. in view of Burbaum et al. further in view of Walker et al. and Ladner et al., a cellular delivery module of a polypeptide as taught by Fischer et al., in order to provide efficient preparation for in vivo analysis of enzyme activity.

Regarding claim 49, Fischer et al. teach the cellular delivery module covalently attached to the one or more molecules (pg. 825, abstract).

With respect to claims 52-54, Fischer et al. teach that the cellular delivery module can also be used as a sub cellular delivery module by directing the proteins associated with the module to the same component (pg. 826, right column), in order to provide more accuracy. Fischer et al. teach the sub cellular delivery module being a polypeptide (pg. 827, right column, second paragraph) and covalently attached to the one or more molecules (pg. 825, abstract).

Regarding claims 50, 51, 55 and 56, Burbaum et al. teach covalently attaching a caging group to a polypeptide in order to control activation of the polypeptide (col. 7, lines 37-47).

Art Unit: 1641

Therefore it would have been obvious to one having ordinary skill in the art at the time the invention was made to include on the cellular delivery modules, a caging group as taught by Burbaum et al., in order to provide control for the time of introduction of the sensor into cellular components.

***Allowable Subject Matter***

6. Claims 26-28 and 33-46 are allowable over the prior art for the reasons stated in the office action dated 16 December 2005.

***Response to Arguments***

7. Applicant's arguments with respect to the pending claims have been considered but are moot in view of the new ground(s) of rejection. The previous rejections of the claims have been withdrawn. However, upon further consideration, a new ground(s) of rejection is made in view of Ladner et al. teaching a protein may be made in vivo or in vitro. Further rejections are made in view of Burbaum et al. in view of Walker et al. further in view of Ting et al., because this rejection does not rely on the peptides of Ting being made in vivo and instead relies only on Ting for the teaching of the advantages of having a kinase substrate in a cell.

***Conclusion***

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Melanie Yu whose telephone number is (571) 272-2933. The examiner can normally be reached on M-F 8:30-5.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Long Le can be reached on (571) 272-0823. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Art Unit: 1641

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02/11/07